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A 'Biogenetic Like' Synthesis of Perloline, 6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[*c*][2,7]naphthyridin-4(3*H*)-one*

Thach Duong, Rolf H. Prager and Stephen T. Were

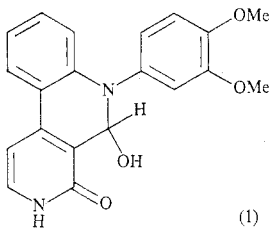
Department of Organic Chemistry, University of Adelaide,
P.O. Box 498, Adelaide, S.A. 5001.

Abstract

9*H*-Indeno[2,1-*c*]pyridine-1(2*H*),9-dione, prepared by a new efficient route, reacts with 3,4-dimethoxyphenyllithium to form the keto alcohol (7), which rearranges with hydrazoic acid to form 5-(3,4-dimethoxyphenyl)benz[*c*][2,7]naphthyridin-4(3*H*)-one. The *N*-oxide photolyses smoothly to yield dehydroperloline as the sole product.

Introduction

Perloline, 6-(3,4-dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[*c*][2,7]naphthyridin-4(3*H*)-one (1), is the major alkaloid of perennial rye grass (*Lolium perenne*)[1] and related species,[2] and has created some interest because of its implication in 'rye grass staggers' of sheep.[3,4] The cause of a similar syndrome in annual rye grass (*Lolium rigidum*) is now understood to be associated with toxins produced by a nematode, *Anguina agrostis* and a bacterium *Corynebacterium rathayi*,[5,6] so the role of perloline must be



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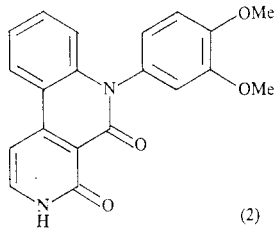

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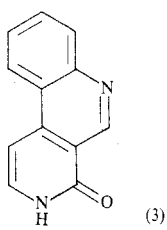

(3)

* Part of this work has been published in preliminary form (Prager, R., Duong, T., and Clarke, S., *Heterocycles*, 1982, **18**, 237).

[1] Melville, J., and Grimmet, R. E. R., *Nature (London)*, 1941, **148**, 782.
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[6] Vogel, P., Petterson, D. S., Berry, P. H., Frahn, J. L., Anderton, N., Cockrum, P. A., Edgar, J. A., Jago, M. V., Lanigan, G. W., Payne, A. L., and Culvenor, C. C. J., *Aust. J. Exp. Biol. Med. Sci.*, 1981, **59**, 455.

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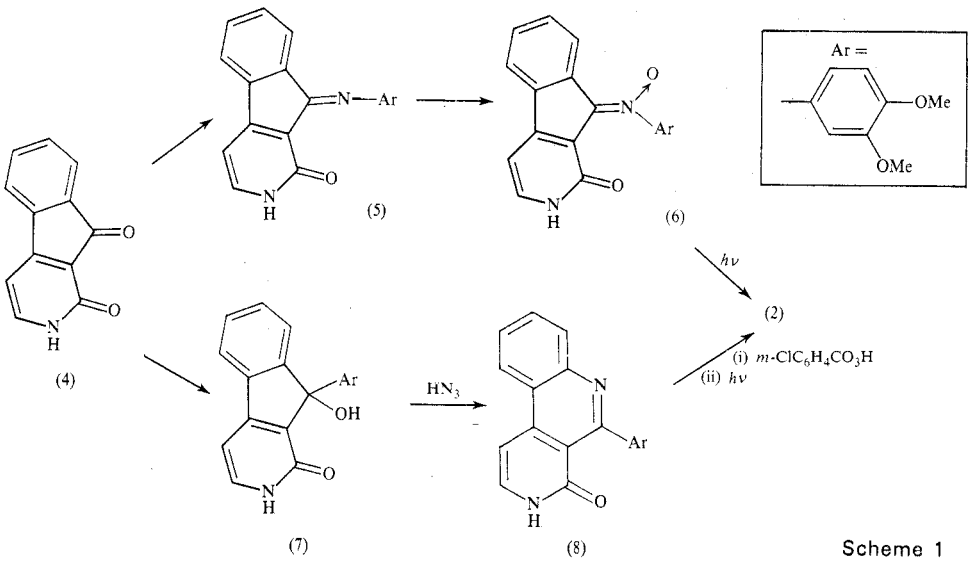
placed in doubt. The structure of perloline has been determined by X-ray analysis.[7] The limited degradative work carried out on perloline resulted in the characterization of an oxidation product, dehydroperloline* (2)[8] and perlolidine† (3), the latter of which has been synthesized by two independent groups.[9,10] The synthesis of the amide (2), which is readily converted into perloline,[11] is the subject of the present communication.

Discussion

In their synthesis of perlolidine, Powers and Ponticello[10] described the synthesis of the diketone (4), and we have investigated two routes for the conversion of (4) into dehydroperloline (2) as shown in Scheme 1. As outlined in a separate communication,[12] we suspected that the biosynthesis of perloline might involve an aryl shift from carbon to nitrogen, as in (8)→(2), and hence our initial synthetic endeavours were modelled on this approach.



Scheme 1

We first investigated possible alternative methods for the preparation of (4), which was available in only low yield by the published procedures.[10,13] The benzoyl pyridinone (10), readily obtained from the oxopyridine-3-carboxylic acid (9), was treated

* 6-(3,4-Dimethoxyphenyl)benzo[*c*][2,7]naphthyridine-4,5(3*H*,6*H*)-dione.
† Benzo[*c*][2,7]naphthyridin-4(3*H*)-one.

[7] Ferguson, G., Jeffreys, J. A. D., and Sim, G. A., *J. Chem. Soc. B*, 1966, 454.
[8] Jeffreys, J. A. D., Sim, G. A., Burnell, R. H., Taylor, W. I., Corbett, R. E., Murray, J., and Sweetman, B. J., *Proc. Chem. Soc. (London)*, 1963, 171.
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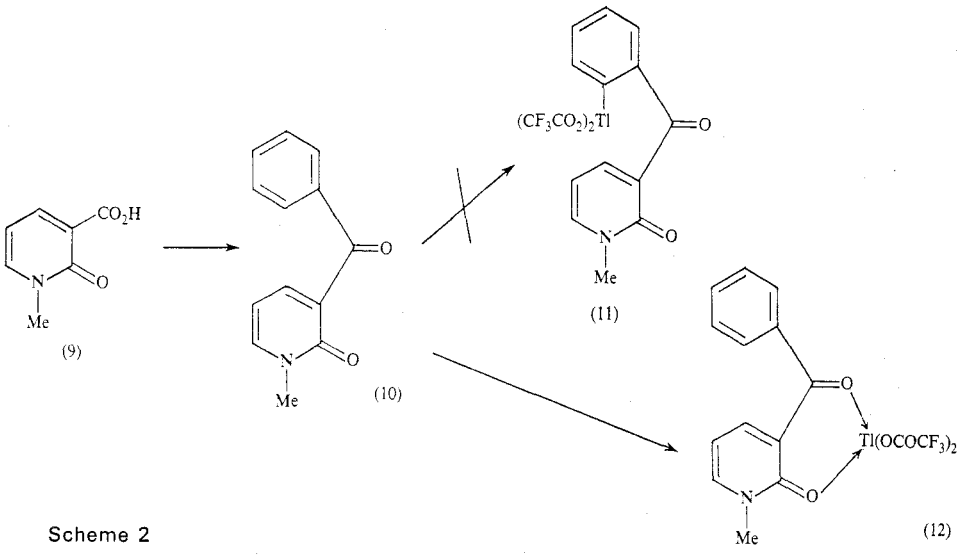
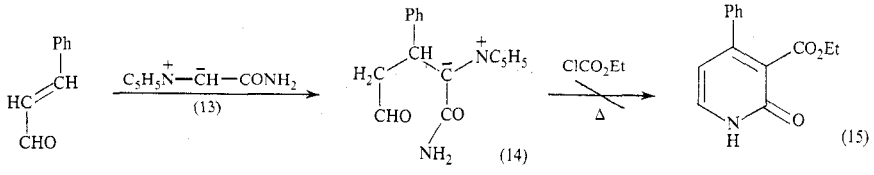
[10] Powers, J. C., and Ponticello, I., *J. Am. Chem. Soc.*, 1968, **90**, 7102.
[11] Prager, R. H., and Were, S., *Aust. J. Chem.*, 1983, **36**, 1441.
[12] Clarke, S. I., and Prager, R. H., *Aust. J. Chem.*, 1982, **35**, 1645.
[13] Bowden, B. F., Picker, K., Ritchie, E., and Taylor, W. C., *Aust. J. Chem.*, 1975, **28**, 2681.

with thallium trifluoroacetate[14] in an attempt to achieve thallation *ortho* to the carbonyl group. It was then hoped to photolyse[15] the intermediate (11) to form the methylated analogue of (4). A thallium adduct was formed, but is believed to have the structure (12), since (10) was recovered after the photolysis (Scheme 2). Photochemical cyclization of (10)[16] was also attempted, but without success.



Scheme 2

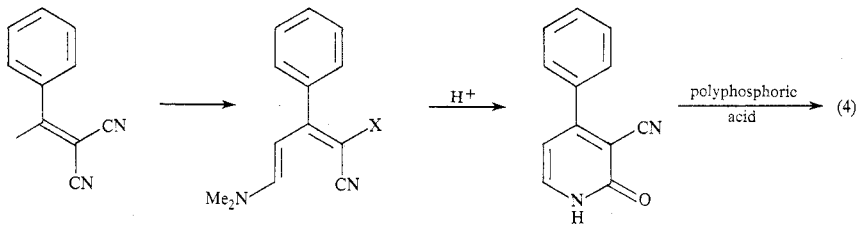
One further unsuccessful sequence is of some interest. The pyridinium ylide (13) has been shown[17] to undergo conjugate additions, for example to cinnamaldehyde to give (14). We have attempted to acylate (14) to the pyridinone ester (15) (Scheme 3), but in keeping with the work of Jeffreys,[9] we find that (14) is too stable to undergo further acylation. Like Kryshtal *et al.*[18] we find that both ethyl cyanoacetate and cyanoacetamide add to cinnamaldehyde only at the aldehyde group. An efficient route to the fluorenone (4) is shown in Scheme 4. 1-Phenylethylidenemalononitrile[19] reacts readily with dimethylformamide dimethyl acetal[20] to give (16), which is cyclized to the cyanopyridinone (17), the precursor of (4).[10] The overall yield in this sequence



Scheme 3

[14] McKillop, A., Fowler, J. S., Zelesko, M. J., Hunt, J. D., Taylor, E. C., and McGillivray, G., *Tetrahedron Lett.*, 1969, 2423.
[15] Taylor, E. C., and Kienzla, K., *J. Am. Chem. Soc.*, 1970, **92**, 6088.
[16] Ninomuya, I., Naito, T., and Mori, T., *Tetrahedron Lett.*, 1969, 3643.
[17] Thesing, J., and Müller, A., *Chem. Ber.*, 1957, **90**, 711.
[18] Kryshtal, G. V., Kul'ganek, V. V., Kucherov, V. F., and Yanovskaya, L. A., *Synthesis*, 1979, 107.
[19] Mowry, D. T., *J. Am. Chem. Soc.*, 1943, **65**, 991.
[20] Ried, W., and Nyiondi-Bonguen, E., *Justus Liebigs Ann. Chem.*, 1973, 1.

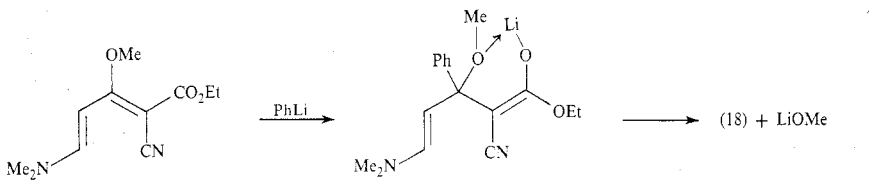
was 75%. Alternatively, ethyl 2-cyano-3-phenylcrotonate was converted into the enamine (18) which was cyclized to the ester (15) in 80% overall yield. The enamine (18) was also prepared in good yield by the reaction of phenyllithium in ether with the enamine (19) (Scheme 5).[21] Presumably displacement of the methoxyl group in this case is facilitated by co-ordination with lithium, as in (20). The procedure for the synthesis of (17), above, has similarities with those of Marecki[22] and Junek.[23] The latter method suffers from a low-yielding step to make (16) and a hydrolysis procedure that leads to mixtures, while the first started with cyanoacetamide, which, in our hands, also gave low yields on reaction with acetophenone.



(16) X = CN
(18) X = CO_2Et

(17)

Scheme 4



(19) (20)

Scheme 5

The fluorenone (4) did not readily form an anil with 3,4-dimethoxyaniline, zinc chloride[24] being a necessary catalyst. Under these conditions the complex (21) was formed, and all attempts to remove the metal resulted in decomposition. Furthermore, the electron density on the azine nitrogen was now too low for reaction to occur with *m*-chloroperbenzoic acid. The successful route involved the reaction of (4) with 3,4-dimethoxyphenyllithium to give (7), followed by reaction with hydrazoic acid in polyphosphoric acid to give (8), accompanied by a trace of (5). The formation of the Grignard reagent from 3,4-dimethoxybromobenzene was extremely capricious, (compare similar difficulties reported in ref.[25]), so its use was avoided.

Since the correctness of the assignment of structure (8) to the Schmidt reaction product is crucial to the synthesis, some discussion of the nature of this reaction is warranted. Three possible modes of rearrangement (*a*,*b*,*c*) of the intermediate protonated azide (22) can be envisaged. The work of Arcus,[26] and our own model studies[12] had defined most of the parameters of this reaction. Thus, although the most electron-rich group migrates to nitrogen in a sulfuric acid medium (in this context, presumably

[21] Kasum, B., and Prager, R. H., *Aust. J. Chem.*, 1983, **36**, 1455.
[22] Marecki, P. E., Wemple, J. N., and Butke, G. P., *J. Heterocycl. Chem.*, 1982, **19**, 1247.
[23] Junek, H., Stolz, G., and Schmidt, A. R. O., *Monatsh. Chem.*, 1971, **102**, 154.
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[25] Feutrill, G. I., and Whitelaw, M. L., *Aust. J. Chem.*, 1981, **34**, 1523.
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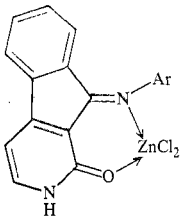

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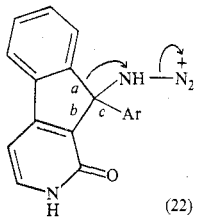

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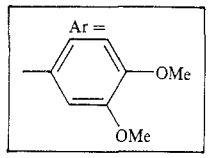

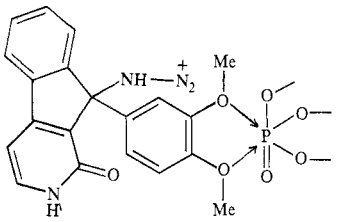

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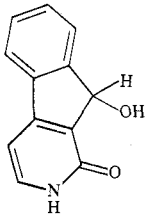

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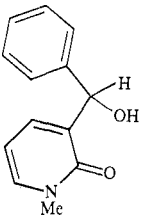
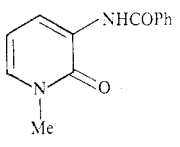


(25)

the dimethoxyphenyl group), in polyphosphoric acid (ppa) ring expansion to the phenanthridine is favoured, possibly due to complexing of the ppa to the methoxy groups, thereby decreasing the aryl migratory aptitude (cf. (23)). We had previously noted strong medium effects associated with the use of ppa in the Schmidt reaction of ketones.[27] In the context of the rearrangement of (22) in ppa, therefore, one had to decide only between pathways *a* and *b*. Powers and Ponticello[10] had shown that in the reaction between hydrazoic acid and the secondary alcohol (24), only the benzene ring (path *a*) migrated. We also have noted that the alcohol (25) gives only the product from benzene ring migration on treatment with hydrazoic acid. Clearly, therefore, the benzene ring has a greater migratory aptitude than the pyridinone ring in the Schmidt reaction of alcohols, and structure (8) is correct. However, the difference in mechanism of alcohols with hydrazoic acid, and ketones with hydrazoic acid, already noted by several groups,[28,29] is well illustrated by the nature of the products from treatment of the ketone (10) with hydrazoic acid. In ppa there was no reaction, but in sulfuric acid the sole product was (26), formed by migration of the pyridinone ring. We suggest that special circumstances prevail in this case; the intermediate (27a) is doubtless of lower energy than (27b), both because of the greater



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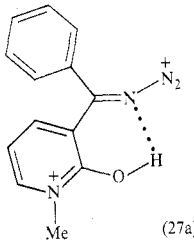

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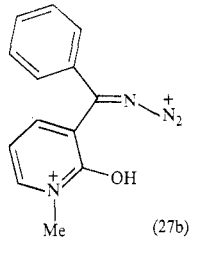

(27b)

[27] Prager, R. H., Tippett, J. M., and Ward, A. D., *Aust. J. Chem.*, 1978, **31**, 1989.
[28] McEwan, W. E., and Mehta, N. B., *J. Am. Chem. Soc.*, 1952, **74**, 526.
[29] Shechter, H., and Kirk, J. C., *J. Am. Chem. Soc.*, 1951, **73**, 3087.

separation of charge, and because of the effect of internal hydrogen bonding, and thus the pyridinone group, *anti* to the departing nitrogen, migrates.

The phenanthridine (8) reacted with *m*-chloroperbenzoic acid[30] to give the *N*-oxide, irradiation[31] of which gave dehydroperloline (2) as the sole product. Again the intermediate oxaziridine[31] could give three products, but by carrying out the rearrangement in ethanol and at longer wavelengths[12] the side reactions were eliminated.* The identity of the dehydroperloline was confirmed by comparison of its spectra with those of an authentic sample, and by direct comparison with a sample that had been reduced to perloline.[11]

Experimental

General details have been given in the first part of this series.[12]

3-Benzoyl-1-methylpyridin-2(1H)-one (10)

1-Methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid[32] (0·153 g; 1 mmol) was added in small portions over half an hour to a stirred solution of oxalyl chloride (1·02 g, 8 mmol) in dry benzene (20 ml) at 20°. The mixture was stirred at room temperature for 3 h, during which time the acid slowly dissolved. The reaction was completed by warming to 50–55° for 30 min. The mixture was cooled, the solvent was removed and the crude acid chloride (ν_{max} 1780 cm^{-1}) was dissolved in benzene (10 ml) at 0°. Aluminium chloride (0·4 g) was added to this solution over 1·5 h, and the reaction mixture allowed to warm to room temperature, then refluxed for 6 h. After cooling, crushed ice (20 g) was added, followed by hydrochloric acid (3 M; 20 ml). The aqueous phase was washed with ether, basified and extracted with chloroform. The combined chloroform extracts were washed with water, dried and filtered; the solvent was removed. Recrystallization of the solid product from ethanol gave (10) as yellow *needles* (0·09 g, 44%), m.p. 114–115° (Found: C, 73·2; H, 5·3; N, 6·5. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2; N, 6·6%). ν_{max} 1645 cm^{-1}. N.m.r. δ 7·9–7·4, m, 7H; 6·20, t, *J* 7 Hz, 1H; 3·50, s, 3H, NMe. Mass spectrum *m/e* 213 (M).

Attempted Cyclization of (10)

(i) *By photolysis.*—Compound (10) (0·10 g) in methanol (200 ml) was irradiated by using a low-pressure mercury lamp in a quartz flask at room temperature for 3 days. Thin-layer chromatography of the reaction mixture showed only unchanged starting material. This reaction was repeated with benzene as solvent in the presence of a little iodine but again no reaction occurred.

(ii) *By thallation.*—A 0·8 M solution of thallium(III) trifluoroacetate (ttfa) in trifluoroacetic acid (tfa) was prepared according to the method of McKillop *et al.*[14]

Compound (10) (0·266 g) was added to ttfa in tfa (7 ml) and the reaction mixture allowed to stand at room temperature overnight. The solvent was removed under reduced pressure, the residual oil was suspended in benzene (200 ml) in a quartz flask under nitrogen and the suspension was then irradiated for 2 days. The benzene solution was evaporated to dryness to give a brown oil which was identified as starting material by t.l.c. and its infrared spectrum.

Attempted Preparation of 2-Oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (17)

(i) Bromocyanoacetamide (2·0 g) was heated with pyridine (4·0 g) for 1 h. To the cooled mixture was added 1 M NaOH (15 ml), methanol (30 ml) and cinnamaldehyde (1·32 g). After 10 min acetic acid (30 ml) was added and, after cooling, the reaction mixture was extracted with benzene. The

* These types of rearrangements have been studied in more detail by Dr W. C. Taylor in Sydney (cf. accompanying paper).

[30] Eckroth, D. R., Kinstle, T. H., De la Cruz, D. O., and Sparacino, J. K., *J. Org. Chem.*, 1971, **36**, 3619.
[31] Taylor, E. C., and Spence, G. G., *J. Chem. Soc., Chem. Commun.*, 1966, 767; 1968, 1037.
[32] Holman, W. J. M., and Weigand, C., *Biochem. J.*, 1968, **43**, 423.

solvent was removed from the dried extract to yield a yellow solid which was identified as 2-cyano-5-phenylpenta-2,4-dienamide (1·75 g, 80%), m.p. 155° (lit.[33] 156°). ν_{max} 3400, 3200, 2220, 1690 cm^{-1}.

(ii) 1-Carbamoyl-4-oxo-2-phenyl-1-pyridiniobutan-1-ide (14) was prepared essentially by the method of Akhtar *et al.*[9] from cinnamaldehyde (3 g). The yellow glass was dissolved in chloroform (50 ml), and ethyl chloroformate (2 ml) and triethylamine (2 ml) were added. The mixture was refluxed for 3 h, washed with water, and the dried organic phase evaporated to give a brown gum (0·6 g), which contained only traces of (17), as judged by its n.m.r. spectrum.

(iii) A solution of 1-phenylethylidenemalononitrile[19] (5 g) in dichloromethane (15 ml) was treated overnight with dimethylformamide dimethyl acetal (4 ml). The mixture was poured down a column of alumina, and eluted with dichloromethane to give *2-(3-dimethylamino-1-phenylprop-2-enylidene)-malononitrile* (16) (4·8 g), m.p. 143–144° (Found: C, 75·1; H, 6·1. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9%). ν_{max} 2200, 1605, 1510 cm^{-1}. N.m.r. δ 7·45, m, 5H; 6·64, d, J 12 Hz, 1H; 5·83, d, J 12 Hz, 1H; 3·05, s, 6H.

The nitrile (16) (1 g) was refluxed for 2 h in trifluoroacetic acid (10 ml), and then diluted with an equal volume of water. The solid (0·9 g) was collected and recrystallized from ethanol as colourless needles, m.p. 231–233°, identical with that of an authentic sample (lit.[10] m.p. 233–234°). ν_{max} 2200, 1655, 1635, 1610 cm^{-1}.

Ethyl 2-Cyano-5-dimethylamino-3-phenylpenta-2,4-dienoate (18)

(i) Ethyl 2-cyano-3-phenylcrotonate[34] (1·42 g, 6·58 mmol) was stirred under nitrogen at 20° and dimethylformamide dimethyl acetal was added. The mixture was stirred until it solidified (1 h) and was then left for a further 2 h. The volatile material was removed under vacuum and the solid which remained was chromatographed on alumina with dichloromethane. The *enamine* (18) was recrystallized as a mixture of isomers from dichloromethane/light petroleum as yellow prisms, m.p. 138–139° (1·65 g, 93%) (Found: C, 71·4; H, 6·5; N, 10·3. $C_{16}H_{18}N_2O_2$ requires C, 71·1; H, 6·7; N, 10·4%). ν_{max} 2200 (CN), 1680, 1615 cm^{-1}. N.m.r. δ 1·10, t, J 7 Hz; 1·33, t, J 7 Hz; 1·45, t, J 7 Hz, 3H; 2·93, s, 6H, 2 × NCH_3; 3·93, q, J 7 Hz; 4·22, q, J 7 Hz, 2H; 5·82, 6·28, AB q, J 12 Hz; 6·38, d, J 14 Hz; 7·0–7·5, m, 7H. Mass spectrum m/e 270 (M), 225 (M − OCH_2CH_3).

(ii) Ethyl 2-cyano-5-dimethylamino-3-methoxypenta-2,4-dienoate[21] (224 mg; 1 mmol) in tetrahydrofuran (10 ml) was stirred with phenyllithium in tetrahydrofuran (0·9 M, 1·1 ml) for 2 h at 20°. Water (10 ml) was added, the mixture was extracted with dichloromethane and the crude product was chromatographed on alumina. Elution with dichloromethane separated the enamine (18) as a mixture of isomers (160 mg) from a small amount of starting material. The n.m.r. and i.r. spectra and t.l.c. properties were identical with those of the sample prepared above.

Ethyl 2-Oxo-4-phenyl-1,2-dihyropyridine-3-carboxylate (15)

The enamine (18) (585 mg, 2·17 mmol) was dissolved in refluxing 80% acetic acid (50 ml). The yellow-green solution was refluxed for 3 h by which time the solution had changed to a dark colour. The solvent was removed under vacuum. The residue was dissolved in dichloromethane (50 ml) and washed with saturated sodium hydrogen carbonate solution (20 ml). The aqueous solution was extracted with dichloromethane (2 × 20 ml), the combined organic extracts were dried and the solvent was removed under vacuum. The solid residue (539 mg) was chromatographed on silica with dichloromethane/acetic acid (90 : 10) which gave the *pyridin-2-one* (15) (461 mg, 87%). Recrystallization from dichloromethane/light petroleum gave (15) as off-white plates, m.p. 183–185° (Found: C, 69·2; H, 5·5; N, 5·9. $C_{14}H_{13}NO_3$ requires C, 69·1; H, 5·4; N, 5·8%). ν_{max} 1735, 1625. ^1H n.m.r. (80 MHz) δ 0·99, t, J 7·5 Hz, 3H; 4·16, q, J 7·5 Hz, 2H; 6·39, d, J 7 Hz, 1H, H 5; 7·44, s, 5H; 7·52, d, J 7 Hz, 1H, H 6. ^{13}C n.m.r. δ 13·7, 61·0, 106·9, 123·9, 127·7, 129·0, 129·5, 136·7, 137·6, 151·5, 160·2, 166·6. Mass spectrum m/e 243 (M), 198 (M − OCH_2CH_3).

Zinc Chloride Complex (21)

A mixture of 9*H*-indeno[2,1-*c*]pyridine-1(2*H*),9-dione (4) (0·30 g), 4-aminoveratrole (0·45 g) and zinc chloride (0·20 g) was refluxed in toluene (50 ml) for 7 days. Filtration of the cooled reaction

[33] Curtis, R. H., Day, J. N. E., and Kimmins, L. G., *J. Chem. Soc.*, 1923, **123**, 3131.
[34] Cope, A. C., Hofmann, C. M., Wyckoff, C., and Hardenbergh, E., *J. Am. Chem. Soc.*, 1941, **63**, 3452.

mixture gave an orange *solid* which was washed with a little cold water or dilute acid. A sample was recrystallized from ethanol (Found: C, 51·4; H, 3·4; N, 6·4. $C_{20}H_{16}Cl_2N_2O_3Zn$ requires C, 51·3; H, 3·4; N, 6·0%). ν_{max} 3100, 1645 cm^{-1}. The complex was dissolved in concentrated acid and the solution was extracted with chloroform. The solvent was removed to give a yellow solid which was identified as the ketone (4) by its n.m.r. and i.r. spectra.

Reaction of (21) with m-*Chloroperbenzoic Acid*

m-Chloroperbenzoic acid (0·80 g) was added to a solution of the *zinc chloride complex* (21) (0·50 g) in chloroform (30 ml) and the resulting mixture stirred at room temperature for 3 days. During this period the solution darkened in colour. The dark solution was then poured through a column of neutral alumina and the eluate evaporated to dryness under reduced pressure to yield a dark oil which polymerized rapidly on standing.

Reaction of 9H-Indeno[2,1-c]pyridine-1(2H),9-dione with 4-Bromoveratrole

(i) Magnesium turnings (1·2 g) were washed with a little sodium-dried ether to remove surface grease, dried at 100–120° and allowed to cool in a desiccator. A portion of a solution of redistilled 4-bromoveratrole (5·40 g) in anhydrous tetrahydrofuran (20 ml) was added to the turnings and the reaction mixture was stirred and heated under nitrogen. To start the reaction, a few drops of redistilled ethyl iodide were added, and when the reaction had commenced, the remainder of the halide was added and the mixture refluxed overnight. After cooling, the reaction was stirred at room temperature for another day. Addition of dry tetrahydrofuran (200 ml) was necessary to keep the Grignard reagent in solution when it was cooled. A solution of the ketone (4) (0·60 g) in dry tetrahydrofuran (30 ml) was added over 2 h to the stirred Grignard reagent at 0°. During this addition the colour changed from yellow to green. The reaction mixture was stirred for another hour at 0° and then left overnight at room temperature when the colour of the reaction changed from green to brown. The reaction was quenched with crushed ice and saturated ammonium chloride. The organic phase was separated and the aqueous phase was extracted with chloroform (3 × 50 ml). The combined extracts were dried, the solvent removed, and the residue recrystallized from ethanol to yield *9-(3,4-dimethoxyphenyl)-9-hydroxy-9H-indeno[2,1-c]pyridin-1(2H)-one* (7) as yellow needles (0·60 g, 63%). A small sample was recrystallized from ethanol before analysis and had m.p. 225° (Found: C, 71·7; H, 5·3; N, 4·1. $C_{20}H_{17}NO_4$ requires C, 71·6; H, 5·1; N, 4·2%). ν_{max} 3250, 3150, 1640 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 7·80–7·20, m, 7H; 6·70, m, 3H; 5·60, b, 1H, OH, exch. D_2O; 3·80, 6H, 2 × OMe. Mass spectrum *m/e* 335 (M).

(ii) The use of 3,4-dimethoxyphenyllithium[12] led to more reproducible reactions, the yield being essentially the same as that above.

1-Methyl-3-(α-hydroxybenzyl)pyridin-2(1H)-one (25)

A solution of sodium borohydride (0·40 g) in ethanol (10 ml) was added to ketone (10) (0·64 g) in ethanol (20 ml). The bright yellow colour of the ketone was discharged by the borohydride to yield a clear colourless solution. After stirring for 30 min, the solution was poured into water and the pH adjusted to 4–5 with 10% HCl. Extraction with chloroform, followed by the usual workup gave the crude *product* which was recrystallized from ether as colourless needles (0·50 g, 70%), m.p. 108–109° (Found: C, 72·6; H, 6·2; N, 6·5. $C_{13}H_{13}NO_2$ requires C, 72·5; H, 6·1; N, 6·5%). ν_{max} 3260, 1640 cm^{-1}. N.m.r. δ 7·40, m, 7H; 6·20, t, *J* 7 Hz, 1H; 5·81, b, 1H, CHOH; 5·08, b, 1H, CHOH, exch. D_2O; 3·60, s, 3H, NMe.

The Schmidt Reaction on (10)

To a stirred suspension of sodium azide (0·80 g) in chloroform (10 ml), cooled in ice, sulfuric acid (98%) (10 ml) was slowly added and the stirring was continued for 30 min at 0°. The ice was replaced by a water bath maintained at 20–25° and a solution of (10) (0·10 g) in chloroform (10 ml) added during 20 min. The reaction mixture was stirred at room temperature overnight and then at 50° for another hour. The mixture was cooled and poured onto ice (75 g). Extraction with chloroform and evaporation gave crude product (0·095 g) which was recrystallized from ether as bright yellow needles (0·075 g, 70%) of *3-benzoylamino-1-methylpyridin-2(1H)-one* (26), m.p. 125–126°

(Found: C, 68·5; H, 5·5; N, 12·0. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3; N, 12·3%). ν_{max} 3320, 1640 cm^{-1}. N.m.r. δ 9·30, b, 1H, NH; 8·60, dd, *J* 7 Hz, 2 Hz, 1H; 8·00, m, 2H; 7·50, m, 3H; 7·10, dd, *J* 7 Hz, 2 Hz; 6·30, t, *J* 7 Hz, 1H; 3·60, s, 3H, NMe.

The Schmidt Reaction on Alcohol (25)

(i) *With hydrazoic acid in concentrated sulfuric acid/chloroform.*—The reaction was carried out similarly to that above but with (25) (0·10 g), concentrated sulfuric acid (10 ml), sodium azide (0·10 g) and chloroform (15 ml). Sublimation of the crude product at 110°/0·4 mm gave pure *1-methyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde* as colourless needles (0·05 g, 70%), m.p. 97–97·5° (Found: C, 60·7; H, 5·1; N, 10·2. $C_7H_7NO_2$ requires C, 61·3; H, 5·1; N, 10·2%). N.m.r. δ 10·50, s, 1H, CHO; 8·18, dd, *J* 7 Hz, 2 Hz, 1H; 7·70, dd, *J* 7 Hz, 2 Hz, 1H; 6·40, t, *J* 7 Hz, 1H; 3·67, s, 3H, NMe.

(ii) *With hydrazoic acid in polyphosphoric acid.*—To a mixture of (25) (0·45 g) in polyphosphoric acid (20 g), sodium azide (0·16 g) was added in small portions over 40 min with slow agitation. The temperature was slowly increased to 50–55° on a water bath, and maintained at this level overnight. The reaction mixture was cooled and then poured onto ice-water. Extraction with chloroform and evaporation gave the crude product which, after recrystallization from ether, afforded the same pyridinone aldehyde (0·26 g, 57%) as shown by t.l.c. and its n.m.r. spectrum. The acid aqueous solution was made alkaline with sodium hydroxide solution and extracted with chloroform. Evaporation of the solvent yielded a brown liquid (0·085 g) which was shown to be aniline by its i.r. and n.m.r. spectra.

1-Methyl-2-oxo-1,2-dihydropyridine-3-carboxanilide

A solution of aniline (2·0 g) in benzene (10 ml) was added to the crude acid chloride prepared from 1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (0·46 g, 3 mmol) in benzene (30 ml) and oxalyl chloride (3·06 g). The mixture was then stirred at room temperature for 10 min, 10% hydrochloric acid added, and the mixture then extracted with benzene. The combined benzene extracts were washed with water (15 ml) and dried; the solvent was removed to give a crude solid (0·52 g) which after recrystallization from benzene/ether afforded the *carboxanilide* as colourless needles (0·48 g, 70%), m.p. 169–170° (Found: C, 68·5; H, 5·4; N, 12·0. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3; N, 12·3%). ν_{max} 3050, 1680 cm^{-1}. N.m.r. δ 12·00, b, 1H, NH; 8·66, dd, *J* 7 Hz, 2 Hz, 1H; 7·70, m, 5H, ArH; 7·30, dd, *J* 7 Hz, 2 Hz, 1H; 6·50, t, *J* 7 Hz, 1H; 3·70, s, 3H, NMe.

The Schmidt Reaction on (7)

To a mixture of (7) (0·06 g) in polyphosphoric acid (1·20 g) was added sodium azide (0·05 g) in small portions over 2 h with slow agitation. The temperature was slowly increased to 45–47° on a water bath and this reaction temperature maintained overnight. The reaction mixture was cooled, poured onto crushed ice, and made alkaline with 50% sodium hydroxide. The solution was then extracted with chloroform (5 × 10 ml). The combined chloroform extracts were dried and evaporated to give a brown solid which after recrystallization from ethanol afforded 5-(3,4-dimethoxyphenyl)benz[*c*][2,7]naphthyridin-4(3*H*)-one (8) as pale pink crystals (0·05 g, 87%), m.p. 280–281° (Found: C, 72·0; H, 4·9; N, 8·3. $C_{20}H_{16}N_2O_3$ requires C, 72·3; H, 4·9; N, 8·4%). ν_{max} 1645, 1628 cm^{-1}. Mass spectrum *m/e* 332 (M). λ_{max} 240 nm (ε 27600); 254 (21600); 268 (15600); 280 (9960); 326 (9600).

Dehydroperloline

(i) The compound (8) (0·03 g) and *m*-chloroperbenzoic acid (0·045 g) were dissolved in chloroform (10 ml) and the mixture was stirred at room temperature for 3 days. The yellow solution was poured through a column of neutral alumina and the eluate evaporated. Recrystallization of the crude product from ethanol gave yellowish needles of the partially hydrated N-*oxide* (0·012 g, 40%), m.p. 273–274° (Found: C, 67·2; H, 4·9; N, 7·3. $C_{20}H_{16}N_2O_4.\frac{1}{2}H_2O$ requires C, 67·3; H, 4·8; N, 7·8%). Mass spectrum *m/e* 348, M. λ_{max} 242 (ε 26800); 280 (9400); 288 (8000); 310 (4500); 364 (6600); 404 (4200).

(ii) The *N*-oxide (0·008 g) in ethanol (400 ml) was exposed to sunlight. After 1 h of irradiation, examination of the solution by ultraviolet spectroscopy gave evidence that most of the starting

material had disappeared. Evaporation of the solvent gave a white solid quantitatively, which crystallized from ethanol as fine needles, m.p. 285–287° (lit. 288°).[8] The ultraviolet and infrared spectra were identical with those of an authentic sample of dehydroperloline, as was its mass spectrum (Found: $M^{+\cdot}$, 348·1099. $C_{20}H_{16}N_2O_4$ requires $M^{+\cdot}$, 348·1109). λ_{max} 238 (ε 28800); 255 (19000); 275 (11000); 340 (8000); 350 (8700); 370 (6000). Mass spectrum *m/e* 348 (M).

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